Published in final edited form as:
Curr Opin Pediatr. 2010 December ; 22(6): 687–695. doi:10.1097/MOP.0b013e32833f56d5.

Holoprosencephaly: recommendations for diagnosis and management

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Abstract

Purpose of review—This review presents recent advances in our understanding and clinical management of holoprosencephaly (HPE). HPE is the most common developmental disorder of the human forebrain and involves incomplete or failed separation of the cerebral hemispheres. The epidemiology, clinical features, causes, diagnostic approach, management, and outcomes of HPE are discussed.

Recent findings—Chromosomal abnormalities account for the most commonly identified cause of HPE. However, there are often unidentifiable causes in patients with nonsyndromic, nonchromosomal forms of HPE. The prevalence of HPE may be underestimated given that patients with mild forms often are not diagnosed until they present with severely affected children. Pregestational maternal diabetes mellitus is the most recognized risk factor for HPE, as supported by recent large-scale epidemiological studies. Genetic studies using microarray-based comparative genomic hybridization technology have resulted in better characterization of important HPE loci.

Summary—HPE encompasses a wide spectrum of forebrain and midline defects, with an accompanying wide spectrum of clinical manifestations. A coordinated, multidisciplinary care team is required for clinical management of this complex disorder. Further research will enable us to better understand the pathogenesis and causes of HPE, and thus to improve the genetic counseling of patients and their families.

Keywords

cyclopia; holoprosencephaly; HPE; midline cleft syndrome; *Sonic Hedgehog*

Introduction

Holoprosencephaly (HPE, OMIM 236100), the most common developmental disorder of the human forebrain, results from a disturbance of the delicate balance of signals required for

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proper separation of the cerebral hemispheres. HPE occurs in approximately one out of 250 conceptuses [1]; however, most fetuses do not survive to term. HPE is estimated to occur in up to one out of 10 000 live and stillbirths [2], though only the minority of patients survive past 1 year [3••]. HPE can be attributed to a number of complex causes, including genetic and environmental factors, with the clinical severity typically correlating with the degree of cerebral malformation. A summary of HPE for the clinician is available as 'flashcards' in Solomon *et al.* [4••].

Classification of cerebral structure

Classification of HPE is based upon the degree of separation of the cerebral hemispheres. The most severe form is alobar HPE, with a complete or nearly complete lack of separation of the cerebral hemispheres and a single-midline ventricle. Less severe is semilobar HPE, in which the anterior hemispheres fail to separate, followed by lobar HPE, in which only the most rostral/ventral aspects of the frontal lobes are not separated. The mildest form of HPE with cerebral malformation is middle interhemispheric variant (MIHV) HPE, in which the posterior frontal and parietal lobes fail to separate (Fig. 1), reviewed in Hahn and Barnes [5••] and Marcorelles and Laquerriere [6•]. Septopreoptic HPE is a mild subtype of lobar HPE, which has recently been described as midline fusion restricted to the septal region or preoptic region of the telencephalon [7]. Additionally, selective depletion of a subset of cortical interneurons has been shown in patients with HPE [8].

Craniofacial and other features

The spectrum of ophthalmologic features ranges, in decreasing severity, from cyclopia (a single central eye) or synophthalmia (two fused eyes in the midline) to hypotelorism with or without colobomata. Nasal/oral features range, in decreasing severity, from a proboscis (nose-like appendage, usually above a cyclopic eye) to a midline cleft lip and/or palate to a depressed nasal bridge, closely spaced nares, and a single maxillary central incisor (SMCI). Microform HPE describes the presence of subtle facial midline features, such as hypotelorism and a SMCI, in the absence of structural brain abnormalities [12••] (Fig. 2) ([9,10,11••]).

HPE can be associated with genetic syndromes, the most common of which is Smith-Lemli-Opitz (OMIM 270400) [13]. In relatively rare instances, subsets of patients may present with additional structural cerebral malformations, such as schizencephaly [14], or extracerebral manifestations, such as ectrodactyly, radial limb defects, agnathia, or craniosynostosis [15–18].

Etiology

Most patients with HPE have chromosomal abnormalities or syndromic forms of HPE, defined as multiple malformation syndromes with a normal karyotype. Such patients have higher perinatal mortality. The majority of living children with HPE have 'nonsyndromic, nonchromosomal HPE', which describes HPE that cannot be attributed to chromosomal or syndromic causes, and includes environmental causes, deletions of or mutations in genes known to be involved in HPE, or currently unidentifiable factors [2,3••,4••].

Nongenetic risk factors and associated variables

HPE is associated with pregestational maternal diabetes. Consistent maternal folic acid use appears to be protective [19]. There are mixed and inconsistent results regarding possible associations between HPE and respiratory illness, anemia, and smoking, and the use of salicylates, antiepileptics, sex hormones, statins, and alcohol [20•].

HPE may be more common in females, nonwhite ethnicities, and in multiple gestation pregnancies; however, the evidence is unclear. Infants with HPE are more likely to be preterm or low birth weight compared with controls [2,19,20•].

Studies of teratogenesis in mice have revealed that the critical period for the induction of HPE corresponds to the 3rd to 4th week after conception in human development. In animal models, HPE can result from exposure to teratogens, such as ethanol, retinoic acid, ochratoxin A (a food-borne mycotoxin), cyclopamine (an inhibitor of Hedgehog signaling), and those that interfere with cholesterol biosynthesis (reviewed in Lipinski *et al.* [21]). Three small molecule inhibitors of Hedgehog relevant to human exposure include tolnaftate (an antifungal agent), ipriflavone (a dietary supplement), and 17-β-estradiol; however, none have been linked to human birth defects [22].

Genetic risk factors

At least 13 different HPE loci, or chromosomal regions, have been identified based on recurrent cytogenic rearrangements, nine of which include known HPE genes [23•]. The primary pathway identified to be disturbed in HPE and related midline defects is the Sonic Hedgehog (SHH) signaling pathway, reviewed in Roessler and Muenke [23•], and Schachter and Krauss [24]. The four most commonly implicated HPE genes include: *Sonic Hedgehog* (*SHH*, OMIM 600725) on 7q36, *ZIC2* (OMIM 603073) on 13q32, *SIX3* (OMIM 603714) on 2p21, and *TGIF* (OMIM 602630) on 18p11.3. For patients with normal karyotypes, approximately 22% have identified point mutations in or microdeletions of the above four genes: *SHH* (at least 6–10%), *ZIC2* (6–8%), *SIX3* (3–5%), and *TGIF* (1–2%) ([25–27]; Muenke M, unpublished data). Additional HPE genes that are less frequently altered include *GLI2* (OMIM 165230) on 2q14 [28], *NODAL* (OMIM 601265) on 10q22.1 [29], and *FGF8* (OMIM 600483) on 10q24 [30], among others.

Abnormalities of chromosome number occur in approximately 32–42% of patients with HPE, most commonly trisomy 13, followed by trisomy 18 and triploidy (reviewed in Solomon *et al.* [31]).

Higher resolution techniques, such as microarray-based comparative genomic hybridization [array CGH (aCGH)], have allowed better delineation of novel chromosomal abnormalities with the aim of identifying new HPE genes. aCGH studies have included both a phenotype-first approach, examining patients with HPE for mutations in or deletions of known HPE genes [32•,33], and a genotype-first approach, studying individuals with deletions of known and candidate HPE loci followed by correlation with the presence or absence of HPE [34•].

Diagnostic work-up

The clinical suspicion of HPE is typically based upon compatible craniofacial features, developmental delay or seizures, or specific endocrinological abnormalities. Diagnostic confirmation follows neuroimaging (high-resolution MRI), a complete physical examination, and a comprehensive family and medical history. Fetal MRI provides better characterization of malformations than prenatal ultrasounds (reviewed in Hahn and Barnes [5••]). However, advances in high-resolution prenatal ultrasound have allowed improved consistency between prenatal ultrasound and postnatal confirmation [35].

Step-by-step recommendations for molecular genetic evaluation are reviewed in Pineda-Alvarez *et al.* [36•]:

1. Cytogenetic studies with a high-resolution karyotype
2. In selected patients, medically indicated tests to assess for syndromes associated with HPE (e.g., elevated 7-dehydro-cholesterol levels in Smith-Lemli-Opitz Syndrome)
3. For patients with abnormal chromosomes, specific cytogenetic abnormalities, such as trisomies 13 and 18 or those with breakpoints near known HPE genes, may help clarify the cause of HPE. More in-depth analysis of breakpoints can be done using sequencing or aCGH.
4. For nonsyndromic patients with normal chromosomes, molecular analysis includes testing of the three genes most commonly implicated in HPE: *SHH, ZIC2*, and *SIX3*. *TGIF* is typically included in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory testing; however, given its low mutation frequency rate, testing is now recommended only in select cases or in specialized testing centers with the requisite expertise.
5. For select patients with pituitary abnormalities and/or polydactyly, *GLI2* testing is also recommended.
6. aCGH and further research studies in select patients

Testing is available through both fee-for-service commercial diagnostic centers and free-of-charge CLIA-certified research laboratories. Parental samples allow determination of inheritance and are helpful for genetic counseling. Participation of families in research studies centered around HPE will enable them to be involved in the state-of-the-art genetic testing while contributing to a better understanding of HPE [36•].

Medical complications and management

Levey *et al.* [3••] present an updated review of common medical problems in children with HPE and the appropriate management, based on previous studies and recent data and observations from the database of the Carter Centers for Brain Research in Holoprosencephaly and Related Malformations. The Carter Centers are a national consortium of five institutions that have been studying patients with HPE for over a decade (Figure 3).

Common medical problems and management include [3••]:

1. Hydrocephalus – Hydrocephalus is a relatively common problem in patients with HPE, with about one-sixth of patients requiring cerebrospinal fluid (CSF) shunt placement. A shunt is more likely to be required in patients with alobar HPE and in patients with hydrocephalus due to dorsal cysts, with the lack of thalamic separation likely blocking egress of CSF from the third ventricle. Treatment of hydrocephalus has the potential to improve developmental and functional outcomes, to reduce irritability, and to avoid a disproportionately large head, which may result in difficulty positioning and caring for the child. Given that patients with HPE typically have microcephaly, hydrocephalus should be suspected when macrocephaly, a normal head circumference, or an increasing head circumference is present.

2. Seizures/epilepsy – About 40% of children have epilepsy requiring treatment, whereas about half have had at least one seizure. The most common type of seizure is a complex partial seizure, and onset usually begins in infancy. A single antiepileptic medication, such as carbamazepine or levetiracetam, is effective for treatment in most children. Hypoglycemia or fluctuations in fluid or electrolyte balances may trigger seizures, particularly fluctuations in sodium level or significant dehydration. A case report describes one patient with HPE and narcolepsy with cataplexy, misdiagnosed as epileptic ‘drop attacks’ [37].

3. Motor impairment – Almost all children with HPE have abnormal muscle tone and impaired coordination to some extent, though this may be minimal in children with MIHV and lobar HPE. Cerebral palsy may be used to describe children with HPE, and, thus, children may benefit from physical and occupational therapy, bracing, and sometimes orthopedic surgery. Oral trihexyphenidyl may reduce dystonia; however, it should not be used in patients at risk for acute narrow-angle glaucoma. An intrathecal baclofen pump may reduce severe spasticity and/or dystonia.

4. Pulmonary issues – Oromotor dysfunction increases the risk for acute aspiration and chronic microaspiration, which may result in recurrent respiratory problems and/or chronic lung disease. More severely affected patients may have central apnea, which likely contributes to their high mortality during the first few months of life. Treatments similar to those used for children with cerebral palsy may be considered, including inhaled beta-agonists, inhaled steroids, assistance with clearing airway secretions, such as suctioning and chest physiotherapy, supplemental oxygen, and consideration of tracheostomy placement. Recommended vaccinations include yearly influenza vaccinations starting at 6 months of age, and consideration of the 23-valent pneumococcal vaccine (Pneumovax 23) after 2 years of age.

5. Gastrointestinal problems – Functional gastrointestinal disorders, particularly poor gastric emptying, gastroesophageal reflux (GER), and constipation, are common, presumably due to abnormal neural regulation. GER may be reduced by acid blockers, adjusting the rate, volume, and schedule of tube feedings and frequent venting of air in children who are tube-fed, prokinetic agents, or by consideration

of surgical interventions such as Nissen fundoplication or gastrojejunostomy. Constipation may be managed by adjusting fluid intake, diet, polyethylene glycol 3350 (MiraLAX), rectal suppositories, and prokinetic agents.

6. Oromotor dysfunction, feeding and nutrition – Almost all children with alobar and semilobar HPE have problems with swallowing, with the degree of impairment often correlating with the degree of motor impairment. Choking, coughing, or gagging during feeds, or increased respiratory symptoms such as wheezing or coughing after feeds, suggest oropharyngeal dysphagia. Speech/language therapy and a gastrostomy tube can reduce the risk of aspiration or inadequate oral intake.

7. Endocrine dysfunction – Central diabetes insipidus is the most common endocrine disorder in children with classic HPE, with a correlation between the degree of diabetes insipidus and the degree of hypothalamic separation. Diabetes insipidus may be treated by DDAVP (desmopressin acetate) and/or fluid management. In addition, hypothyroidism, hypoadrenocorticism, growth hormone deficiency, and other endocrine disorders may occur. It is recommended that endocrine function be evaluated during the neonatal period, with a low threshold for repeat evaluations. Hypoglycemia, poor feeding, poor linear growth, lethargy, and apnea may indicate anterior pituitary hormone insufficiency. Caregivers should be educated about diabetes insipidus or adrenocorticotropic hormone crises/decompensations, which can be life-threatening, particularly in conjunction with an acute illness.

8. Hypothalamic dysfunction – Hypothalamic dysfunction may be due to the lack of separation of hypothalamic nuclei, and results in abnormal sleep–wake cycles, temperature instability, and impaired thirst mechanisms. Abnormal sleep–wake cycles may be managed by establishing good sleep hygiene, melatonin, or by bedtime administration of an already-prescribed medication with sedative effects, such as an antiepileptic. Temperature instability can usually be managed by modifying a child's environment and by avoiding moderate to severe hypothermia (<33–34°C) or hyperthermia (>40–41°C). Abnormal fluctuations in a child's usual temperature range suggest illness. Signs of relative hypothermia include lethargy, low heart rate and blood pressure, and decreased respirations. Signs of relative hyperthermia include increased seizures and irritability.

9. Ophthalmologic problems – Cortical visual impairment is common, and thus therapy services for the visually impaired may be beneficial. Strabismus may be treated with penalization (patching or drops) of the good eye, eyeglasses, or surgery. Rarely, surgery for ptosis may be required [Levey EB, unpublished data; Muenke M, unpublished data].

10. Craniofacial-related complications – Cleft lips and/or palates may be surgically repaired or accommodated by special nipples. Upper airway obstruction may result from facial anomalies.

11. Follow-up – A primary medical provider, whether a geneticist, neonatologist, pediatric neurologist, developmental pediatrician, or primary care pediatrician, is essential for closely following the child, for coordinating care and for providing a

balanced and realistic prognosis for the child. Routine childcare and evaluation and treatment of acute illnesses are also important.

Outcomes

Survival and developmental outcomes are reviewed in Levey *et al.* [3••]. Mortality is high in newborns with HPE. However, some children survive beyond the neonatal period, including a smaller number of children who survive into adulthood. The group of patients with the greatest survival includes children with isolated HPE or with no associated chromosomal abnormality or syndrome. Although survival typically correlates with the severity of brain malformation, there is significant survival variability within each type of HPE.

Virtually all children with HPE have developmental disabilities, the degree of which typically relates to the severity of the brain malformation on neuroimaging. Children with alobar HPE can develop early infantile skills; overall, however, they have profound global impairment and make minimal developmental progress. Children with semilobar HPE follow a broader spectrum of outcomes that may range from little developmental progress to significant cognitive and language skills. Speech development is typically limited by severe motor impairment. Children with lobar and MIHV HPE develop better motor and speech skills. The Carter Neurocognitive Assessment (CNA) is a tool that may be used to assess cognitive abilities in such patients, whose motor and expressive language impairments limit the use of traditional developmental assessments [3••].

Genotype–phenotype correlation

SHH is the most commonly identified disease-causing gene in patients with nonsyndromic, nonchromosomal HPE. Patients with *SHH* mutations display variable expressivity, with nearly half presenting with structural brain anomalies. Large families often segregate *SHH* mutations with high penetrance, though the mutation may only be identified after the diagnosis of a severely affected child, who may be identified prenatally [12••].

Patients with *ZIC2* mutations display a distinctive phenotype with bitemporal narrowing, upslanting palpebral fissures, a short nose with anteverted nares, a broad and well demarcated philtrum, and large ears. Alobar and semilobar types are overrepresented. Most *ZIC2* mutations are *de novo* [38••].

Patients with *SIX3* mutations tend to have more severe HPE than other patients with nonsyndromic, nonchromosomal HPE. Mutations often segregate in large families [11••,39]. Mutations in *SHH, ZIC2*, and *SIX3* are either predicted or confirmed to be loss-of-function, or related to insufficient gene product [27,40,41].

Though the numbers are small, patients with intragenic *TGIF* mutations are less likely to have structural brain abnormalities compared with those with *ZIC2* and *SIX3* mutations. Patients with *TGIF* deletions are more likely to have extra-neuronal/craniofacial findings, likely related to the deletion of additional genes on 18p. Intragenic mutations are more likely to be inherited compared with whole gene deletions (Keaton AA *et al*., in preparation).

Interestingly, only a fraction of patients with 18p deletions, and presumably loss of one copy of *TGIF*, present with HPE [42].

Patients with *GLI2* mutations have a characteristic phenotype that can include defective anterior pituitary formation and pan-hypopituitarism, HPE-like midfacial hypoplasia, and polydactyly, with or without forebrain cleavage abnormalities [28].

Overall genotype–phenotype correlation is reviewed in Solomon *et al.* [12••].

Genetic counseling

Misinformation about HPE and its treatment and prognosis continues to be present among healthcare providers. It is important for pediatricians and obstetricians to accurately discuss the spectrum of clinical outcomes with families making decisions regarding pregnancy and medical care [43•].

Genetic counseling should include a thorough clinical evaluation, including phenotypic assessment of the parents and prenatal history, given the heterogeneity of the causes and manifestations of HPE. Prenatal molecular testing of an inherited mutation should be considered alongside fetal imaging and with cautious interpretation given the lack of strict genotype–phenotype correlations. Further recommendations reviewed in Mercier *et al.* [44].

Overall, inheritance of nonsyndromic HPE is primarily autosomal dominant, with a high but incomplete penetrance and a high rate of sporadic cases. For apparently sporadic cases, recurrence risk is estimated at 13% for major forms, and 14% when including minor forms [45].

While discussing the experiences and perceived needs of parents of children with HPE, Stashinko *et al.* [43•] describe that ‘living with a child with HPE requires balancing hopes and realistic expectations’ (p. 198). Furthermore, their recommendations include combating myths and misconceptions with knowledge and hope, encouraging parents to network, focusing on the child’s strengths and positive qualities, and developing realistic goals.

Resources for families include local genetic counseling centers; tertiary care centers, such as The Carter Centers for Brain Research in Holoprosencephaly and Related Malformations (http://www.stanford.edu/group/hpe/) and the National Institutes of Health; and support groups, such as Families for HoPE, Inc. (http://familiesforhope.org/).

Conclusion

The pathogenesis of HPE is complex, as are the care and management of patients with HPE. Coordinated, multidisciplinary care can help ensure that a child receives optimal treatment. Given that multiple factors likely contribute to this disorder, further research is required, facilitated by the participation of physicians, patients, and relatives of patients in research studies. This allows better delineation of the phenotypic spectrum and variability of HPE and improved understanding of the functional significance of genetic heterogeneity observed with given genetic alterations.

Acknowledgments

We appreciate the many families who have enabled physicians and researchers to advance our understanding of holoprosencephaly. Thank you to Erich B. Levey, MD (Kennedy Krieger Institute), Benjamin D. Solomon, MD (National Human Genome Research Institute), and Daniel E. Pineda-Alvarez, MD (National Human Genome Research Institute) for their invaluable assistance with the manuscript, and to the Carter Centers for Brain Research in Holoprosencephaly and Related Malformations. Thank you to Jin S. Hahn, MD (Stanford University School of Medicine) for contributing the MRI images.

This research was supported by the Division of Intramural Research, National Human Genome Research Institute, National Institutes of Health, Department of Health and Human Services, United States of America.

Funding has been received from the National Institutes of Health.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 834–835).

1. Shiota K, Yamada S. Early pathogenesis of holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010; 154C:22–28. [PubMed: 20104600]
2. Orioli IM, Castilla EE. Epidemiology of holoprosencephaly: prevalence and risk factors. Am J Med Genet C Semin Med Genet. 2010; 154C:13–21. [PubMed: 20104599]
3. Levey EB, Stashinko E, Clegg NJ, Delgado MR. Management of children with holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010; 154C:183–190. [PubMed: 20104615] The authors of this article are clinicians and researchers in the Carter Centers for Brain Research in Holoprosencephaly and Related Malformations. This article provides a very thorough and valuable resource for clinicians who care for children with HPE as it reviews the clinical management and outcomes of children with HPE.
4. Solomon BD, Pineda-Alvarez DE, Mercier S, et al. Holoprosencephaly flashcards: a summary for the clinician. Am J Med Genet C Semin Med Genet. 2010; 154C:3–7. [PubMed: 20104594] This article provides a summary for clinicians of key information about HPE, in the format of ‘flashcards’. The flashcards illustrate the prevalence, causes, and types of HPE, as well as the craniofacial and neurological findings, physical examination features, the clinical approach, and resources.
5. Hahn JS, Barnes PD. Neuroimaging advances in holoprosencephaly: refining the spectrum of the midline malformation. Am J Med Genet C Semin Med Genet. 2010; 154C:120–132. [PubMed: 20104607] This article is a valuable resource for understanding the spectrum of HPE specifically as it relates to neuroimaging. The article thoroughly describes the cerebral structure of each type of HPE, with accompanying neuroimages and labels to highlight key features.
6. Marcorelles P, Laquerriere A. Neuropathology of holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010; 154C:109–119. [PubMed: 20104606] This article provides a thorough description of the neuropathology associated with the spectrum of HPE, complemented by images of pathological specimens.
7. Hahn JS, Barnes PD, Clegg NJ, Stashinko EE. Septopreoptic holoprosencephaly: a mild subtype associated with midline craniofacial anomalies. AJNR Am J Neuroradiol. 2010 [Epub ahead of print].
8. Fertuzinhos S, Krsnik Z, Kawasawa YI, et al. Selective depletion of molecularly defined cortical interneurons in human holoprosencephaly with severe striatal hypoplasia. Cereb Cortex. 2009; 19:2196–2207. [PubMed: 19234067]

9. Roessler E, Belloni E, Gaudenz K, et al. Mutations in the human Sonic Hedgehog gene cause holoprosencephaly. Nat Genet. 1996; 14:357–360. [PubMed: 8896572]
10. Ming JE, Kaupas ME, Roessler E, et al. Mutations in PATCHED-1, the receptor for SONIC HEDGEHOG, are associated with holoprosencephaly. Hum Genet. 2002; 110:297–301. [PubMed: 11941477]
11. Lacbawan F, Solomon BD, Roessler E, et al. Clinical spectrum of SIX3-associated mutations in holoprosencephaly: Correlation between genotype, phenotype and function. J Med Genet. 2009; 46:389–398. [PubMed: 19346217] This article represents the largest comprehensive evaluation of patients with mutations in *SIX3*. The phenotypic analysis reveals that *SIX3* mutations result in relatively severe HPE, the severity can be correlated with genotype based upon a mutation-specific functional assay in zebrafish.
12. Solomon BD, Mercier S, Velez JI, et al. Analysis of genotype-phenotype correlations in human holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010; 154C:133–141. [PubMed: 20104608] This article is a valuable resource for clinicians and genetic counselors to better understand the correlation between genotype and phenotype in HPE. For each known HPE gene, the paper summarizes the characteristic phenotype, the typical mode of inheritance, and the penetrance. This is followed by a statistical analysis of the spectrum of mutations and structural brain anomalies.
13. Weaver DD, Solomon BD, Akin-Samson K, et al. Cyclopia (synophthalmia) in Smith-Lemli-Opitz Syndrome: first reported case and consideration of mechanism. Am J Med Genet C Semin Med Genet. 2010; 154C:142–145. [PubMed: 20104611]
14. Hehr U, Pineda-Alvarez DE, Uyanik G, et al. Heterozygous mutations in SIX3 and SHH are associated with schizencephaly and further expand the clinical spectrum of holoprosencephaly. Hum Genet. 2010; 127:555–561. [PubMed: 20157829]
15. Dane B, Dane C, Aksoy F, Yayla M. Semilobar holoprosencephaly with associated cyclopia and radial aplasia: first trimester diagnosis by means of integrating 2D–3D ultrasound. Arch Gynecol Obstet. 2009; 280:647–651. [PubMed: 19221775]
16. Kauvar EF, Solomon BD, Curry CJ, et al. Holoprosencephaly and agnathia spectrum: presentation of two new patients and review of the literature. Am J Med Genet C Semin Med Genet. 2010; 154C:158–169. [PubMed: 20104613]
17. Keaton AA, Solomon BD, van Essen AJ, et al. Holoprosencephaly and ectrodactyly: report of three new patients and review of the literature. Am J Med Genet C Semin Med Genet. 2010; 154C:170–175. [PubMed: 20104609]
18. Raam MS, Solomon BD, Shalev SA, Muenke M. Holoprosencephaly and craniosynostosis: a report of two siblings and review of the literature. Am J Med Genet C Semin Med Genet. 2010; 154C:176–182. [PubMed: 20104614]
19. Miller EA, Rasmussen SA, Siega-Riz AM, et al. Risk factors for nonsyndromic holoprosencephaly in the National Birth Defects Prevention Study. Am J Med Genet C Semin Med Genet. 2010; 154C:62–72. [PubMed: 20104597]
20. Johnson CY, Rasmussen SA. Non-genetic risk factors for holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010; 154C:73–85. [PubMed: 20104598] This article provides a summary of the non-genetic risk factors for HPE based on case reports and case series, animal studies, and epidemiologic studies from four case–control studies, including the Kyoto Embryo Study, the California Birth Defects Monitoring Program, the Latin American Study of Congenital Malformations, and the National Birth Defects Prevention Study.
21. Lipinski RJ, Godin EA, O'Leary-Moore SH, et al. Genesis of teratogen-induced holoprosencephaly in mice. Am J Med Genet C Semin Med Genet. 2010; 154C:29–42. [PubMed: 20104601]
22. Lipinski RJ, Bushman W. Identification of Hedgehog signaling inhibitors with relevant human exposure by small molecular screening. Toxicol In Vitro. 2010; 24:1404–1409. [PubMed: 20434536]
23. Roessler E, Muenke M. The molecular genetics of holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010; 154C:52–61. [PubMed: 20104595] This article reviews the molecular genetics of HPE, including the history of how the HPE genetic loci were mapped, the role of model organisms in understanding development, and how midline and forebrain development proceeds.

24. Schachter KA, Krauss RS. Murine models of holoprosencephaly. Curr Top Dev Biol. 2008; 84:139–170. [PubMed: 19186244]
25. Bendavid C, Dubourg C, Gicquel I, et al. Molecular evaluation of foetuses with holoprosencephaly shows high incidence of microdeletions in the HPE genes. Hum Genet. 2006; 119:1–8. [PubMed: 16323008]
26. Dubourg C, Lazaro L, Pasquier L, et al. Molecular screening of SHH, ZIC2, SIX3, and TGIF genes in patients with features of holoprosencephaly spectrum: mutation review and genotype-phenotype correlations. Hum Mutat. 2004; 24:43–51. [PubMed: 15221788]
27. Roessler E, El-Jaick KB, Dubourg C, et al. The mutational spectrum of holoprosencephaly-associated changes within the SHH gene in humans predicts loss-of-function through either key structural alterations of the ligand or its altered synthesis. Hum Mutat. 2009; 30:E921–E935. [PubMed: 19603532]
28. Roessler E, Du YZ, Mullor JL, et al. Loss-of-function mutations in the human GLI2 gene are associated with pituitary anomalies and holoprosencephaly-like features. Proc Natl Acad Sci U S A. 2003; 100:13424–13429. [PubMed: 14581620]
29. Roessler E, Pei W, Ouspenskaia MV, et al. Cumulative ligand activity of NODAL mutations and modifiers are linked to human heart defects and holoprosencephaly. Mol Genet Metab. 2009; 98:225–234. [PubMed: 19553149]
30. Arauz RF, Solomon BD, Pineda-Alvarez DE, et al. A hypomorphic allele in the FGF8 gene contributes to holoprosencephaly and is allelic to gonadotropin-releasing hormone deficiency in humans. Mol Syndromol. 2010; 1:59–66. [PubMed: 21045958]
31. Solomon BD, Rosenbaum KN, Meck JM, Muenke M. Holoprosencephaly due to numeric chromosome abnormalities. Am J Med Genet C Semin Med Genet. 2010; 154C:146–148. [PubMed: 20104610]
32. Bendavid C, Rochard L, Dubourg C, et al. Array-CGH analysis indicates a high prevalence of genomic rearrangements in holoprosencephaly: an updated map of candidate loci. Hum Mutat. 2009; 30:1175–1182. [PubMed: 19431187] This is the first aCGH study to examine a large cohort of patients with HPE. The study reveals a high frequency of submicroscopic anomalies and updates the map of HPE candidate loci.
33. Bendavid C, Dupe V, Rochard L, et al. Holoprosencephaly: an update on cytogenetic abnormalities. Am J Med Genet C Semin Med Genet. 2010; 154C:86–92. [PubMed: 20104602]
34. Rosenfeld JA, Ballif BC, Martin DM, et al. Clinical characterization of individuals with deletions of genes in holoprosencephaly pathways by aCGH refines the phenotypic spectrum of HPE. Hum Genet. 2010 [Epub ahead of print]. This aCGH study examines a large cohort of individuals with deletions of known and candidate HPE loci, followed by correlation with the presence or absence of HPE. The study supports the hypothesis that the interaction of multiple genetic and environmental factors is required to result in HPE.
35. Wenghoefer M, Ettema AM, Sina F, et al. Prenatal ultrasound diagnosis in 51 cases of holoprosencephaly: craniofacial anatomy, associated malformations, and genetics. Cleft Palate Craniofac J. 2010; 47:15–21. [PubMed: 19860496]
36. Pineda-Alvarez D, Dubourg C, David V, et al. Current recommendations for the molecular evaluation of newly diagnosed holoprosencephaly patients. Am J Med Genet C Semin Med Genet. 2010; 154C:93–101. [PubMed: 20104604] This article provides updated recommendations for the molecular evaluation of patients with HPE, including a step-by-step algorithm.
37. Plazzi G, Tonon C, Rubboli G, et al. Narcolepsy with cataplexy associated with holoprosencephaly misdiagnosed as epileptic drop attacks. Mov Disord. 2010; 25:780–782.
38. Solomon BD, Lacbawan FL, Mercier S, et al. Mutations in ZIC2 in human holoprosencephaly: description of a novel ZIC2-specific phenotype and comprehensive analysis of 157 individuals. J Med Genet. 2010; 47:513–524. [PubMed: 19955556] This article describes the characteristic phenotype of patients with HPE and ZIC2 mutations, and reveals how *ZIC2*-related HPE differs from HPE due to other causes given its lack of typical facial dysmorphisms. The study also emphasizes the importance of examining other organ systems in patients with HPE, not only those ‘above-the-neck’.

39. Solomon BD, Lacbawan F, Jain M, et al. A novel SIX3 mutation segregates with holoprosencephaly in a large family. Am J Med Genet A. 2009; 149A:919–925. [PubMed: 19353631]

40. Domene S, Roessler E, El-Jaick KB, et al. Mutations in the human SIX3 gene in holoprosencephaly are loss of function. Hum Mol Genet. 2008; 17:3919–3928. [PubMed: 18791198]

41. Roessler E, Lacbawan F, Dubourg C, et al. The full spectrum of holoprosencephaly-associated mutations within the ZIC2 gene in humans predicts loss-of-function as the predominant disease mechanism. Hum Mutat. 2009; 30:E541–E554. [PubMed: 19177455]

42. Turleau C. Monosomy 18p [review]. Orphanet J Rare Dis. 2008; 3:4. [PubMed: 18284672]

43. Stashinko EE, Harley LA, Steele RA, Clegg NJ. Parental perspectives on living with a child with HoPE. Am J Med Genet C Semin Med Genet. 2010; 154C:197–201. [PubMed: 20104617] This article is a great resource for parents of children with HPE and for clinicians. It describes the experiences and perceived needs of a small group of parents, in conjunction with discussing literature relevant to the care of children with HPE.

44. Mercier S, Dubourg C, Belleguic M, et al. Genetic counseling and ‘molecular’ prenatal diagnosis of holoprosencephaly (HPE). Am J Med Genet C Semin Med Genet. 2010; 154C:191–196. [PubMed: 20104616]

45. Odent S, Le Marec B, Munnich A, et al. Segregation analysis in nonsyndromic holoprosencephaly. Am J Med Genet. 1998; 77:139–143. [PubMed: 9605287]

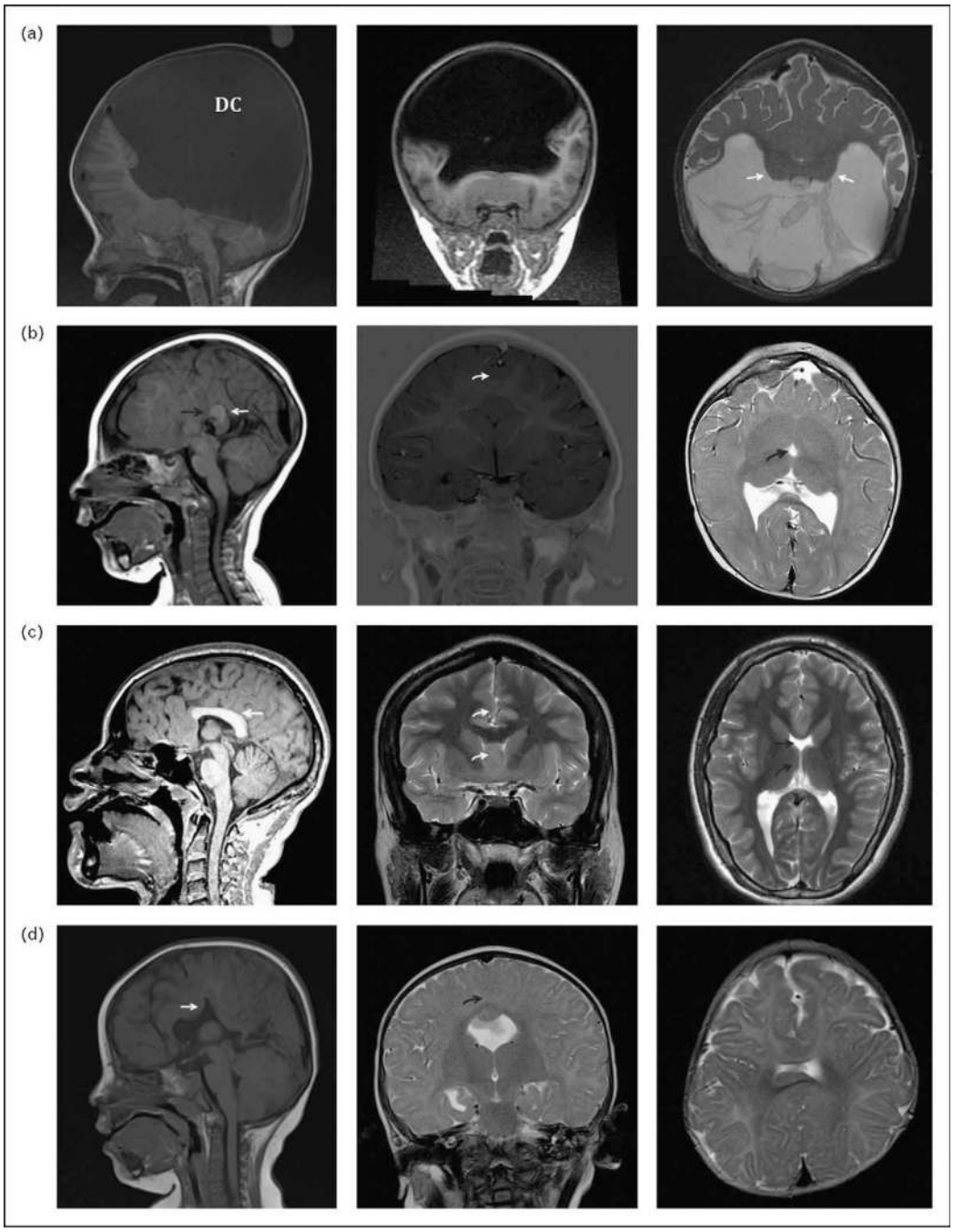

Figure 1. The neurological spectrum of holoprosencephaly

Sagittal, coronal, and axial MRI images (left to right, respectively) depict the spectrum of HPE, from the most severe form, alobar HPE (a), to the mildest form middle interhemispheric variant (MIHV) HPE (d). (a) MRI of a 10-month-old infant with alobar HPE that shows entire hemispheric fusion, an absent falx cerebri, an absent corpus callosum, a monoventricle, a large dorsal cyst (DC) with massive hydrocephaly, and a central gray mass that consists of poorly differentiated caudate and lentiform nuclei fused in the midline (white arrows). (b) MRI of an 8-month-old infant with semilobar HPE that shows anterior

hemispheric fusion (curved white arrow), a present posterior falx cerebri, absent frontal horns (curved black arrow), and absence of the genu of the corpus callosum (black arrow), but presence of the splenium and some of the posterior body (white arrow). (c) MRI of an 18-year-old individual with lobar HPE that shows fusion of the deep mesial and basal frontal lobes (superior curved white arrow) and continuous gray matter in the basal frontal region (inferior curved white arrow), a full falx cerebri, a small frontal horn (black arrow), an absent head of the corpus callosum with the body and splenium present (white arrow), and separation of the caudate and lentiform nuclei (curved black arrow). (d) MRI of a 10-month-old infant with MIHV HPE that shows midfrontal hemispheric fusion (curved black arrow) and an absent body of the corpus callosum that puckers superiorly due to cortical fusion (white arrow). Images courtesy of Jin S. Hahn, MD of Stanford University School of Medicine, Lucile Packard Children's Hospital, and Stanford Carter Center for Brain Research in Holoprosencephaly and Related Malformations.

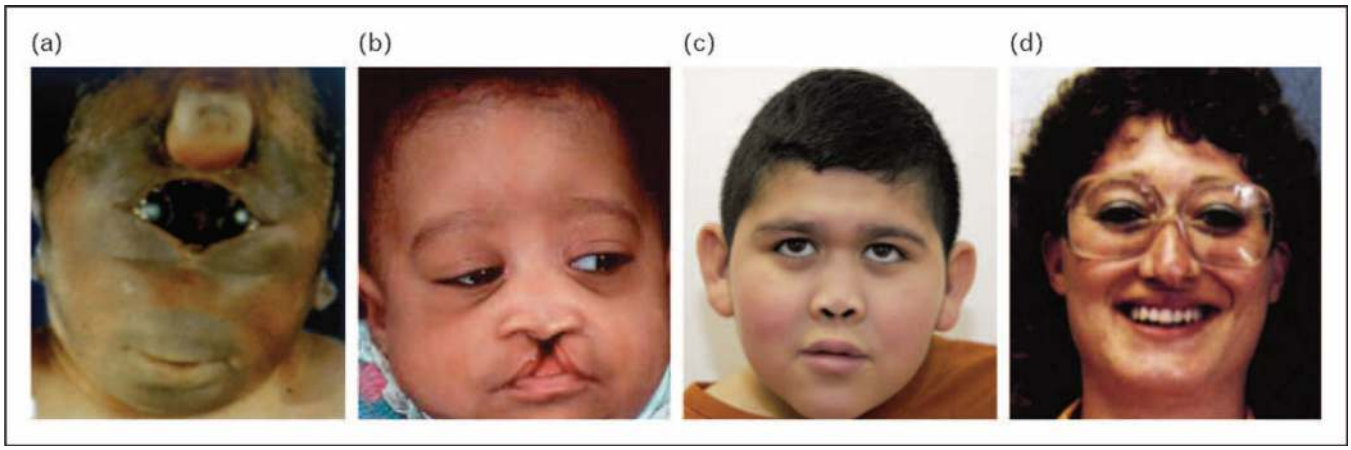

Figure 2. The craniofacial spectrum of holoprosencephaly

The spectrum of HPE ranges from the most severe form, alobar HPE (a), to the mildest form, microform HPE (d) (left to right, respectively). (a, b) Two patients with alobar HPE who have different degrees of craniofacial involvement: (a) a patient with synophthalmia (two eyes fused) and a proboscis (nose-like structure); (b) a patient with hypotelorism, a flat nasal bridge, colobomata, and a facial cleft; (c) a patient with lobar HPE, who has hypotelorism and a flat nasal bridge; (d) a patient with microform HPE, who has hypotelorism and a single maxillary central incisor. Images modified and reproduced with permission from the following: (a,d) from [9], Nature Publishing Group; (b) from [10], Springer Science+Business Media, Fig. 1c; and (c) from [11••], BMJ Publishing Group, Ltd.

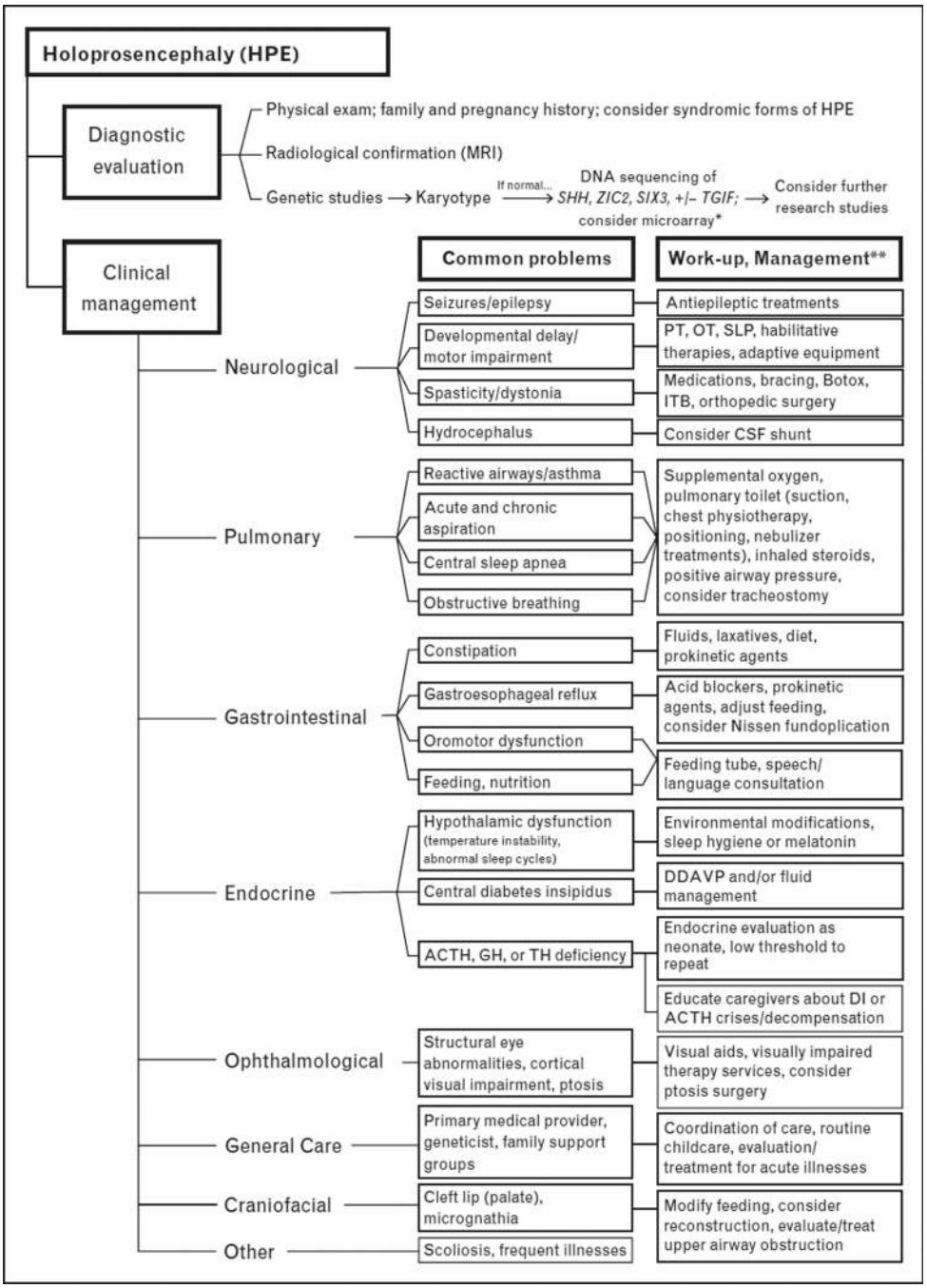

Figure 3. The diagnostic evaluation and clinical management of children with holoprosencephaly

The illustrated flowchart summarizes the recommended approach for the diagnostic evaluation and clinical management of children with HPE. *See Pineda-Alvarez *et al.* [36•] for further details on the molecular evaluation. **See Levey *et al.* [3••] for further details on clinical problems and management. Clinical work-up and management should be guided by the primary care physician and appropriate consultative specialties. The above list is not intended to be exhaustive or comprehensive, and it may not be applicable to all patients. ACTH, adrenocorticotropic hormone; CSF, cerebrospinal fluid; DDAVP, desmopressin

acetate; DI, diabetes insipidus; GH, growth hormone; ITB, intrathecal baclofen; PT, physical therapy; OT, occupational therapy; SLP, speech/language pathology; TH, thyroid hormone.